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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,823	02/09/2004	Katharine Helen Banner	PC25578A	9233

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PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
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GROTON, CT 06340

EXAMINER	
MONTANARI, DAVID A	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 09/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,823	BANNER ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-15 is/are pending in the application.

4a) Of the above claim(s) 2,12 and 13 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,3-11,14 and 15 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 2/09/2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 05/13/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-15 are pending.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1, 3-11, and 14-15, drawn to a method of inducing IBD-like symptoms in a mammal, wherein the mammal is a non-human mammal not expressing a function of the mdr1a gene, and is subjected to elevated chlorine concentrations, a method of screening a candidate compound for its efficacy in ameliorating the symptoms of IBD using said non-human mammal, a method of screening a candidate compound for its efficacy in preventing or delaying the development of IBD using said non-human mammal, and a method of screening for genes, by RNA expression profiling, that may be involved in the pathogenesis of IBD using said non-human mammal, classified in class 800, subclass 3.

II. Claims 2, 3-11, and 14-15, drawn to a drawn to a method of inducing IBD-like symptoms in a mammal, wherein the mammal is treated with an inhibitor of the mdr1a gene, and is subjected to elevated chlorine concentrations, a method of screening a candidate compound for its efficacy in ameliorating the symptoms of IBD using said mammal, a method of screening a candidate compound for its efficacy in preventing or delaying the development of IBD using said mammal, and a method of screening for genes, by RNA expression profiling, that may be

involved in the pathogenesis of IBD using said mammal, classified in class 514, subclass 44.

III. Claim 12, drawn to a method of screening for genes that may be involved in IBD, said method comprising using microarray analysis, classified in class 435, subclass 287.2.

IV. Claim 13, drawn to a method of identifying the human homologue of an identified gene that may be involved in IBD, classified in class 424, subclass 9.1+.

Groups I and II are distinct. Group I is drawn to a method of inducing IBD-like symptoms in a non-human mammal, wherein said non-human mammal lacks expression of the mdr1a gene, and methods of using said non-human mammal. Group II is drawn to a method of inducing IBD-like symptoms in a mammal wherein said mammal is treated with an inhibitor of the mdr1a gene and methods of using said mammal. The method of inducing IBD-like symptoms in group I would require materially different and separate protocols from the method of group II. The non-human mammal of group I could be a transgenic knockout animal that would require a significantly different method of implementation compared to the mammal of group II could be developed using anti-sense technology.

Groups I and III are distinct. Group I is drawn to a method of inducing IBD-like symptoms in a non-human mammal, wherein said non-human mammal lacks expression of the mdr1a gene, and methods of using said non-human mammal, and a method of screening for genes involved in the pathogenesis of IBD using RNA expression profiling.

Group III is drawn to a method of screening for genes using the non-human mammal of group I using microarray analysis. The method of screening for gene involved in the pathogenesis of IBD in group I would require materially different and separate protocols of the method of screening for genes in group III.

Groups I and IV are distinct. Group I is drawn to a method of inducing IBD-like symptoms in a non-human mammal, wherein said non-human mammal lacks expression of the mdr1a gene, and methods of using said non-human mammal, and a method of screening for genes involved in the pathogenesis of IBD using RNA expression profiling. Group IV is a method of identifying the human homologue of an identified gene that may be involved in IBD. The method of identifying the human homologue of a gene identified, of group IV, to be involved in the pathogenesis of IBD using the method of group I would require materially separate and distinct protocols.

Groups II and III are distinct. Group II is drawn to a method of inducing IBD-like symptoms in a mammal wherein said mammal is treated with an inhibitor of the mdr1a gene, methods of using said mammal, and a method of screening for genes involved in the pathogenesis of IBD using RNA expression profiling. Group III is drawn to a method of screening for genes using the mammal of group II using microarray analysis. The method of screening for gene involved in the pathogenesis of IBD in group II would require materially different and separate protocols of the method of screening for genes in group III.

Groups II and IV are distinct. Group II is drawn to a method of inducing IBD-like symptoms in a mammal wherein said mammal is treated with an inhibitor of the mdr1a gene, methods of using said mammal, and a method of screening for genes involved in the pathogenesis of IBD using RNA expression profiling. Group IV is a method of identifying the human homologue of an identified gene that may be involved in IBD. The method of identifying the human homologue of a gene identified, of group IV, to be involved in the pathogenesis of IBD using the method of group I would require materially separate and distinct protocols.

Groups III and IV are distinct. Group III is drawn to a method of screening for genes involved in the pathogenesis of IBD using microarray analysis. Group IV is a method of identifying the human homologue of an identified gene that may be involved in IBD. The method of group IV does not require the use of microarray analysis to identify the human homologue of a gene that may be involved in the pathogenesis of IBD.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper. The examiner would be required to search distinct and different areas of art with regard to examination of claims 1-15.

During a telephone conversation with Frank Forman on 8/16/2005 a provisional election was made without traverse to prosecute the invention of Group I, claims 1, 3-11, and 14-15.

Affirmation of this election must be made by applicant in replying to this Office action. Claims 2, and 12-13 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

2. Claims 1,3-11, and 14-15 are examined in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-11, and 14-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing IBD-like symptoms in a transgenic mdr1a deficient mouse, wherein said mouse is subjected to a chlorine concentration of 5ppm or greater in bottled drinking water, a method of screening a candidate compound for its efficacy in ameliorating the symptoms of IBD using the transgenic mouse, a method of screening a candidate compound for its efficacy in preventing or delaying the development of IBD, and a method of screening for genes that may be involved in IBD pathogenesis, does not reasonably provide enablement for a method of inducing IBD-like symptoms in any non-human mammal not expressing a function of the mdr1a gene, that is subjected to any elevated chlorine concentration, a method of screening a candidate compound for its efficacy in ameliorating the symptoms of IBD, a method of screening a candidate compound for its efficacy in preventing or delaying the development of IBD, and a method of screening for genes, by RNA expression profiling. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 3-11, and 14-15 are drawn to a method of inducing IBD-like symptoms in a mammal, wherein the mammal is a non-human mammal not expressing a function of the mdr1a gene, and is subjected to elevated chlorine concentrations, a method of screening a candidate compound for its efficacy in ameliorating the symptoms of IBD, a method of screening a candidate compound for its efficacy in preventing or delaying the development of IBD, and a method of screening for genes, by RNA expression profiling, that may be involved in the pathogenesis of IBD.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the

state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompass using any non-human mammal not expressing a functional mdr1a gene product in a method of inducing IBD-like symptoms using any level of chlorine concentration.

Whereas the nature of the invention is a method of creating a representative human model of IBD symptoms in a animal model and using said animal model for drug and gene screening for compounds and genes involved in IBD, the art teaches that such a method would be unpredictable. The instantly claimed methods encompass using any non-human mammal not expressing a functional mdr1a gene product, however at the time of filing only transgenic mice were known to not express a functional mdr1a gene product. Further the art teaches that the creation of other non-human mammals other than mice lacking a function mdr1a gene product would be unpredictable. The art teaches that transgenic mouse lines are generated by microinjection of the linear DNA of interest into the nucleus of an oocyte or transfected into embryonic stem (ES) cells, which then randomly integrates into the genome (Ristevski, Molecular Biotechnology, Vol. 29, 2005, pg. 159 col. 1 parag. 2 lines 1-5). Currently only mouse ES cells have been established that result in a transgenic animal (Smith, 2002, J. of Biotechnology, Vol. 99, pg. 3 col. 1, parag. 4 lines 1-3). With regard to transgene integration the art teaches that the site of integration is uncontrolled and yet is critical due to the possibility of integration into a silent locus. Random integration may occur, resulting in the insertional inactivation (insertional mutagenesis) of a gene at the site of integration, resulting in a loss of function that may be mistakenly attributed to over expression of the transgene (Ristevski, pg. 159

col. 1 parag. 2 lines 5-14). Further, insertional mutagenesis of a gene may not be immediately apparent if a recessive gene has been inactivated, as phenotypic abnormalities will not be evident until homozygous transgenic lines have been established (Ristevski, pg. 159 col. 1 parag. 2 lines 14-19). The site of integration may also result in altered tissue specificity, although the promoter used behaves differently at its normal chromosomal localization, with neighboring regulatory elements potentially influencing the transcriptional activity of the transgene (Ristevski, pg. 159 col. 1 parag. 3 lines 1-7). This is known as chromosomal position effects, where host sequences surrounding the site of transgene integration can alter the expected expression pattern, turning it ectopic or not detectable (Montoliu, 2002, Cloning and Stem Cells, Vol. 4, pg 39, col. 1). With regard to copy number the art teaches that controlling the transgene copy number (usually integration is a singular event with multiple copies integrated in tandem) is also problematic in the generation of transgenic animals (Ristevski, pg. 159 col. 1 parag. 3 lines 7-11). A high tandem copy number results in a gene silencing effect, and further, is undesirable if the effect of a gene dosage is being addressed, as multiple copies will not recapitulate relevant levels of expression (Ristevski, pg. 159 col. 1 parag. 3 lines 11-14 bridge col. 2 parag. 1). With regard to transgene expression, the art teaches bluntly that, "many transgenes work poorly" (Houdebine, 2002, J. of Biotechnology, Vol. 98, pg. 150, col. 1 parag. 4 line 1). Transgene expression is often very low or not specific of the promoter added in the gene construct, and are generally attributed to position effects in chromatin as discussed above (Houdebine, pg. 150, col. 1 parag. 4 lines 1-5). The art continues to teach that a transgene is generally poorly expressed when it contains a cDNA rather than the corresponding genomic DNA sequence with its introns, has multiple copies integrated in the same site, and when a bacterial gene is used (Houdebine, pg. 150 col. 2

lines 4-9). Overexpression of a transgene of interest also has inherent problems. This is often the case when the overproduced protein shares only a part of the properties of an endogenous protein, which can result in inhibition of the endogenous protein, by the transgene of interest working in a transdominant negative manner (Houdebine, pg. 152, col. 2 parag. 4). The art continues that the generation of transgenic animals routinely involves one of two methods of exogenous DNA delivery to the recipient cells, retroviral infection or microinjection (Smith, pgs. 5-11). However, each method possesses significant unpredictability for the skilled artisan to implement. Retroviral vectors result in inconsistency and irreproducibility of transgene expression due to random integration with host DNA (Smith, pg. 6, col. 1 parag. 2), and instability due to the integrated retroviral DNA possessing the ability to spontaneously reactivate (Smith, pg. 6, col. 1 parag. 5). Microinjection of recipient cells with exogenous DNA presents the problem of mosaicism to the skilled artisan. The majority (≈ 85%) of pronuclear microinjection-derived transgenic founders are mosaics of transgenic and non-transgenic cells (Smith, pg. 7, col. 2 parag. 2 lines 1-4). This becomes problematic since transmission of the transgene is dependent upon the existence and extent of germline colonization by transgene-containing cells, so that when transmission does occur, the transgene is inherited in a mendelian fashion resulting in only a small portion of the transgene being passed onto offspring (Smith, pg. 7, col. 2 parag. 3, bridge pg. 8 col. 1 lines 1-8). Significant restraints also exist for the skilled artisan attempting microinjection of other animal species other than mouse. Cow, pig, and sheep eggs are optically opaque, unlike mice, which makes microinjection of the targeted pronuclei extremely difficult (Smith, pg. 11 col. 2 parag. 1). With regard to elevated chlorine concentrations the art teaches that chlorine concentrations can be elevated in normal drinking

water. The 1999 drinking water quality report of the City of Hamilton and Region of Hamilton-Wentworth teaches that chlorine is added to raw water to prevent growth of bacteria and to keep filters clean (pg. 1). The report continues to teach that sulphur dioxide is added to filtered water to lower chlorine to residual levels of 0.85 to 1.0ppm (pg. 1). If residual levels of chlorine are at 0.85 to 1.0ppm, and they can be higher do to chlorination treatment, the skilled artisan would not be able to differentiate between the IBD-like symptoms in experimental animals receiving elevated chlorine levels in drinking water and control animals also receiving drinking water that may have elevated chlorine levels. In view of the art summarized above, the skilled artisan at the time of filing would surmise that the field of transgenesis is very unpredictable, and thus would require and undo amount of experimentation without a predictable degree of success to implement the claimed method using any non-human mammal other than mouse.

The working examples provided by the instant application teach that forty male mdr1a deficient mice (strain FVB.129-*Pgy3*^{tml} N7) and six control male mice were used in the claimed methods (pg. 11 lines 19-21). The transgenic mice and control mice received a constant dose (5ppm) of chlorine through drinking water (pg. 11 lines 24-26). The chlorine treated transgenic mice had a significant increase in colitis compared to chlorine treated control mice (pg. 18, table 4), with colons from chlorine treated control mice appearing normal, and colons from chlorine treated transgenic mice having lesions that are similar to those of human IBD (pg. 18 lines 7-8). However the specification has failed to teach using any non-human mammal other than mouse in a method of inducing IBD-like symptoms. The specification teaches only the mdr1a deficient mouse which is an establish mouse model of IBD. Further the specification teaches only, that at least 5ppm of chlorine in bottled drinking water, is required to further increase symptoms of IBD

in transgenic mice to more closely represent the symptoms of human IBD. However, as the art teaches, chlorine is present at some levels in drinking water at residual levels, and thus bottled water would be required by the skilled artisan to implement the claimed method to prevent any false phenotype data due to the presence of residual chlorine in non-bottled drinking water.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the claimed invention is not enabled for its full breadth and limiting the scope of the claimed invention to a method of inducing IBD-like symptoms in a transgenic mdr1a deficient mouse, wherein said mouse is subjected to a chlorine concentration of 5ppm or greater in bottled drinking water, a method of screening a candidate compound for its efficacy in ameliorating the symptoms of IBD using the transgenic mouse, a method of screening a candidate compound for its efficacy in preventing or delaying the development of IBD, and a method of screening for genes that may be involved in IBD pathogenesis is proper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Panwala et al. (1998, J. of Immunology, Vol. 161, pgs. 5733-5744) in view of Internet Posting at IBD/IBS Archive (Nov. 28, 1999, http://www.holisticat.com/ibd_arch.html).

Claims 1, 3, and 5-7 are directed to a method of inducing IBD-like symptoms in a mammal, wherein the mammal is a non-human mammal not expressing a function of the mdr1a gene, and is subjected to elevated chlorine concentrations, wherein the elevated chlorine concentrations are administered by supply of chlorinated drinking water to the mammal, wherein the mammal is a transgenic mdr1a$^{-/-}$ knockout mouse, wherein IBD-like symptoms occur in about 100% of the mammals and a method of screening a candidate compound for its efficacy in ameliorating the symptoms of IBD.

Panwala et al. teach that transgenic mice comprising a disruption of the mdr1a gene is an animal model of IBD (pg. 5733, Abstract). Panwala continues to teach that it has been well established in a majority of mouse models that spontaneous colitis can be prevented if mice are housed under germfree conditions, suggesting that the presence of the gut flora is necessary for the development of colitis (pg. 5740, col. 1 parag. 1). Panwala continues to teach that the incidence of colitis in mdr1a deficient mice treated with antibiotics was greatly reduced compared with mdr1a deficient mice treated with saccharine alone (pg. 5740 col. 1 parag. 2 lines 1-3). Panwala does not teach a method of treating mdr1a deficient mice with elevated chlorine concentrations.

The IBD/IBS archive at http://www.holisticat.com/ibd_arch.html teaches that chlorine in typical drinking water kills normal flora and allows for proliferation of non-beneficial bacteria that exacerbates IBD/IBS problems (see posting Jan 6/99). This posting was available to the general public on November 28th, 1999 as evidenced by its last modification to the web page on said date by using WayBack Machine at http://web.archive.org. The IBD/IBS archive does not teach a method of inducing IBD-like symptoms in a mammal.

Thus the ordinary artisan at the time of filing would have been motivated by the teachings of the IBD/IBS archive to modify the method taught by Panwala et al. to subject mdr1a deficient mice, which are an animal model of IBD, to elevated chlorine concentrations since it was known at the time of filing that chlorine in drinking water exacerbates IBD symptoms. Further motivation is provided by Panwala et al. to screen for a candidate compound for efficacy in ameliorating the symptoms of IBD, given Panwala et al. teaching that antibiotics reduce colitis in mdr1a deficient mice. Thus, the cited art provides the requisite teachings and motivation to make and use the claimed invention.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 1-571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 1-571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A. Montanari, Ph.D

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER